REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds.

With this amendment, Claims 28-31, 34-37 and 39-43 have been canceled without prejudice and Claims 32-33, 38, 44 and 46 have been amended.

Claims 32, 33, 38 and 44-47 are pending after entry of the present amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Support for the amendments to Claim 32 can be found in Example 149 at least on page 511-512 of the specification.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

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Information Disclosure Statement

Applicants respectfully thank the Examiner for considering the Information Disclosure Statement filed on November 7, 2002.

Specification

As requested by the Examiner, the specification has been amended to remove embedded

hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Claim Rejections – 35 U.S.C. §101

Claims 28-47 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants respectfully submit that the cancellation of Claims 28-31, 34-37 and 39-43 renders the rejection of these claims moot.

Applicants further submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that Claims 32, 33, 38 and 44-47 possess a specific and substantial asserted utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In

explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

Applicants rely on the adipocyte glucose/FFA uptake assay (Example 149, Assay #94) for support of patentable utility.

The adipocyte glucose/FFA uptake assay is designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids in adipocyte cells. By making such determinations, the assay identifies polypeptides that are expected to be useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is expected to be therapeutically effective. Examples of these types of disorders

include obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1760 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1760 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1760 resulted in less than 0.5 the uptake of the insulin control, PRO1760 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay as described in Example 149 of the instant application was also well known in the art at the time of the effective filing date of the instant application. Similar assays were commonly used to identify potential anti-diabetic agents and study the regulatory mechanisms of important molecules involved in fat cell metabolism.

For example, at the time of the effective filing date of the instant application, it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al.*, *Endocrinology*, 133(1):352-359 (1993) - copies enclosed). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, at the time of the effective filing date of the instant application, vanadium salts were considered as a possible treatment for diabetes, and several clinical trials had already been

performed. (page 26617, right column, Glodwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed). Using the rat adipocyte culture system similar to the system disclosed in the instant application, Glodwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. This is further evidence that at the effective filing date of the present application one skilled in the art would have reasonably expected that molecules activating glucose uptake would find utility in the treatment of diabetes and related diseases.

In addition, the investigators in Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2):551-558 (1998) - copy enclosed). Figure 1A shows the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggest that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and the increase in leptin was closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect on leptin secretion of two well-known anti-diabetic agents, metformin and vanadium, which were known to enhance the glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed). The experimental data indicated that both metformin and vanadium increased glucose uptake and inhibit leptin secretion from cultured adipocytes.

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO1760, that are capable of modulating glucose uptake have a substantial, practical,

real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify the therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1760 based on the glucose/FFA uptake assay results disclosed herein.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1760. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejection - 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 28-47 stand rejected under 35 U.S.C. §112, first paragraph, since "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art clearly would not know how to use the claimed invention." In particular the Examiner asserts that "the specification does not teach any variant, fragment, or derivative of the PRO1760 nucleic acid other than the full-length nucleic acid sequence of SEQ ID NO:375. The specification also does not teach functional or structural characteristics of the nucleic acid variants, fragments, and derivatives recited in the claims."

Applicants respectfully disagree and traverse the rejection.

Applicants respectfully submit that the cancellation of Claims 28-31, 34-37 and 39-43 renders the rejection of these claims moot.

While not acquiescing in the propriety of this rejection, and solely in the interest of furthering prosecution, Applicants have amended Claim 32 (and, as a consequence, those claims dependent from the same) to recite, "the nucleic acid encodes a polypeptide that inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general

knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection - 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-32 and 41-47 are also rejected under 35 U.S.C. §112, first paragraph, allegedly "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner asserts that the claims are drawn to a nucleic acid having at least 80%, 85%, 90%, 95%, or 99% nucleic acid sequence identity to a nucleic acid encoding a polypeptide of SEQ ID NO:376, but that the claims do not require that the nucleic acid possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.

Applicants respectfully disagree and traverse the rejection.

Applicants respectfully submit that the cancellation of Claims 28-31 and 41-43 renders the rejection of these claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Claim 32 (and, as a consequence, those claims dependent from the same) has been amended to recite a functional limitation that "the nucleic acid encodes a polypeptide that inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells." Accordingly, it is no longer true that the claims are drawn to a genus of nucleic acids that is defined only by sequence identity. This biological activity, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession

of the invention claimed at the effective filing date of this application. The Examiner is therefore respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection - 35 U.S.C. §112, Second Paragraph

Claims 28-34, 36-37 and 41-47 are rejected under 35 U.S.C. §112, second paragraph, allegedly "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner objects to the Applicant's use of the terms "extracellular domain" and "lacking its associated signal peptide." The Examiner further asserts that the use of the term "stringent conditions" in Claim 42 fails to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods. Finally, regarding Claim 46, the Examiner alleges that "it cannot be determined if the host cell encompasses an isolated or cultured cell or a transgenic organism."

Applicants respectfully submit that the cancellation of Claims 28-31, 34, 36-37 and 41-43 renders the rejection of these claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the terms "extracellular domain" and "extracellular domain ... lacking its associated signal peptide" are no longer present in Claims 32-33 (and, as a consequence, those claims dependent from the same). Further, Claim 46 has been amended to recite, "An isolated host cell comprising the vector of Claim 44." Hence, the rejection of Claims 32-33 and 44-47 is believed to be moot, and should be withdrawn.

Claim Rejection - 35 U.S.C. §102

Claims 28-31 and 41-47 are rejected under 35 U.S.C. §102(e) as being anticipated by Ruben *et al*, U.S. Patent No. 6,475,753 (effective priority date of June 16, 1998). Examiner asserts that "Ruben *et al.* teach an isolated nucleic acid having at least 95.9% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO:375 of the instant application."

Applicants submit that the cancellation of Claims 28-31 and 41-43 renders the rejection of these claims moot. Furthermore, Claim 44 (and, as a consequence, those claims dependent

from the same) has been amended to be dependent on Claim 32.. Thus, the rejection of Claims 44-47 is believed to be moot, and should be withdrawn.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C66**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 26, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

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